# Efficacy of exercises in early-stage Parkinson's disease (PARK-EASE trial): single-blind, randomised, controlled trial

Raktim Swarnakar ![ORCID],[1] Sanjay Wadhwa,[1] Srikumar Venkataraman,[1] Vinay Goyal,[2] Sreenivas Vishnubhatla[3]

[1]Department of Physical Medicine and Rehabilitation (PMR), All India Institute of Medical Sciences (AIIMS), New Delhi, Delhi, India
[2]Department of Neurology, All India Institute of Medical Sciences (AIIMS), New Delhi, Delhi, India
[3]Department of Biostatistics, All India Institute of Medical Sciences (AIIMS), New Delhi, Delhi, India

**Correspondence to**
Professor Sanjay Wadhwa;
wadhwadr@gmail.com

## ABSTRACT

**Objectives** To assess the efficacy of exercises in early-stage Parkinson's disease (PD).
**Design** Single-blind, randomised controlled trial.
**Setting** Tertiary rehabilitation care centre.
**Participants** Forty individuals (≥18 years, either gender) with newly diagnosed PD (Hoehn and Yahr stage ≤2) on a stable dose of PD medications were randomised (1:1) to the intervention group (IG) and control group (CG).
**Interventions** The IG received strengthening (30 min/day, 2 days/week), aerobic (30 min/day, 3 days/week) and agility (30 min/day, 2 days/week) exercises in a structured format for 12 weeks. CG received stretching exercises for 12 weeks.
**Main outcome measures** Unified PD Rating Scale (UPDRS) III (motor) at week 12 (primary), UPDRS I (mentation, behaviour and mood), UPDRS II and VI (Schwab and England Activities of daily living Scale) and Parkinson's Disease Quality of Life (PDQL) at week 12 (secondary).
**Results** 36 participants completed 12-week study period. UPDRS III (lesser scores reflect improvement) at 12 weeks showed a significant between-group difference (−5.05 points (95% CI: −9.38 to −0.71), p=0.02). At 4 and 8 weeks, UPDRS III did not show a statistically significant between-group difference (−2.15 points (95% CI: −6.77 to 2.47) and −4.1 points (95% CI: −8.54 to 0.34), respectively). From baseline to 12 weeks, UPDRS III in the IG showed a 6.5-point (95% CI (4.85 to 8.14)) reduction, and the CG showed a 0.8-point increase (95% CI (−3.06 to 1.46)), PDQL (higher scores reflect improvement) in the IG showed a 8.45-point (95% CI (−12.78 to −4.11)) increase and CG showed a 2.75-point (95% CI (0.16 to 5.33)) reduction.
**Conclusions** Structured exercises improve motor symptoms and quality of life in early-stage PD. Consistent adherence for at least 12 weeks is crucial for clinical improvement. Early initiation of exercises as neurorehabilitation is recommended. Further research on specific types, dosing and intensity of exercises with a larger sample size is warranted in early-stage PD.
**Trial registration number** CTRI/2018/05/014241.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exercises are found to be beneficial in advanced stages of Parkinson's disease (PD) but studies are lacking especially in early-stage PD.

## WHAT THIS STUDY ADDS

⇒ Exercises in a structured format for 12 weeks are effective in improving motor symptoms and quality of life in early-stage PD. Clinically significant improvement is evident after a minimum of 12 weeks of adherence to exercises.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study (PARK-EASE trial) showed that exercises should be prescribed in a structured format soon after diagnosis of PD. Institution of exercises as early neurorehabilitation along with proper surveillance for adherence to exercises in early-stage PD is recommended. This study would give directions regarding further research on types, doses and intensity of exercises in early-stage PD. Additionally, this study adds evidence for multidisciplinary decision-making for early-stage PD which perhaps would influence policy-making in healthcare (in geriatric rehabilitation or neurorehabilitation in broader sense).

## INTRODUCTION

Parkinson's disease (PD), the second most common neurodegenerative disorder, affects more than 10 million people globally,[1] with a prevalence of 400–1900 cases per 100 000 people.[2] Additionally, improved healthcare has influenced longer survival, leading to an increased prevalence of PD over time.[3]

Management of PD consists of pharmacological and non-pharmacological approaches. Among non-pharmacological approaches, home-based exercises are found to be more accessible and cost-effective.[4] Studies have found that moderate and strenuous exercises are associated with a significantly decreased incidence of developing PD, although this is not a universal finding.[5–7] Animal studies indicated that neuroprotective effects of exercise could delay the progression of PD.[8] Exercise

also may increase the efficacy of pharmacological treatments.[9] However, a recent review found that there was 'insufficient evidence' to support prescribing exercise in newly diagnosed PD.[10] Studies are lacking to comment on the efficacy of exercise in early-stage PD, which is defined as from onset of motor symptoms to motor fluctuations or levodopa-induced dyskinesia.[11 12] We did this study to address present needs, fill the gap and gather evidence for furthering future research.

This is a randomised, controlled, single-blind trial (PARK-EASE trial). Our primary objective was to evaluate the effectiveness of exercises by assessing the Unified PD Rating Scale (UPDRS) III at 12 weeks, and secondary outcome measures were the UPDRS I, II and VI and PD Quality of Life (PDQL) at 12 weeks.[13 14]

## METHODS
### Trial registration and informed consent
The study was performed according to the standards of the 1964 Declaration of Helsinki. All participants gave written informed consent before their inclusion. This study conforms to all Consolidated Standards of Reporting Trials (CONSORT) guidelines and reports the required information accordingly (online supplemental file 1).

### Design
This is a single-centre, single-blind, randomised controlled trial (PARK-EASE) that randomly assigned 40 participants to two groups (CONSORT flow diagram, figure 1). The intervention group (IG) received 12-week structured exercises, and another group served as a control group (CG). The primary objective was to evaluate the effectiveness of exercises by assessing UPDRS III (motor section) at 12 weeks.

### Participants
Participants were recruited from the Movement Disorder Clinic of a tertiary care hospital, and the study was conducted in the rehabilitation care setting of the same hospital (June 2018–October 2019). A neurologist specialising in movement disorders (not involved in group allocation and assessments) recruited the participants. Participants were considered eligible if they were ≥18 years and diagnosed with PD by the UKPD Society Brain Bank Criteria (UKPDSBBC).[15] They were recruited on fulfilling the inclusion and exclusion criteria after filling out informed written consent forms (in Hindi and/or English). Inclusion criteria of the study were: age ≥18 years; either gender; newly diagnosed (by UKPDSBBC) with idiopathic PD (Hoehn and Yahr (H&Y) stage 1 or 2) within 3 years of study participation; and patients who
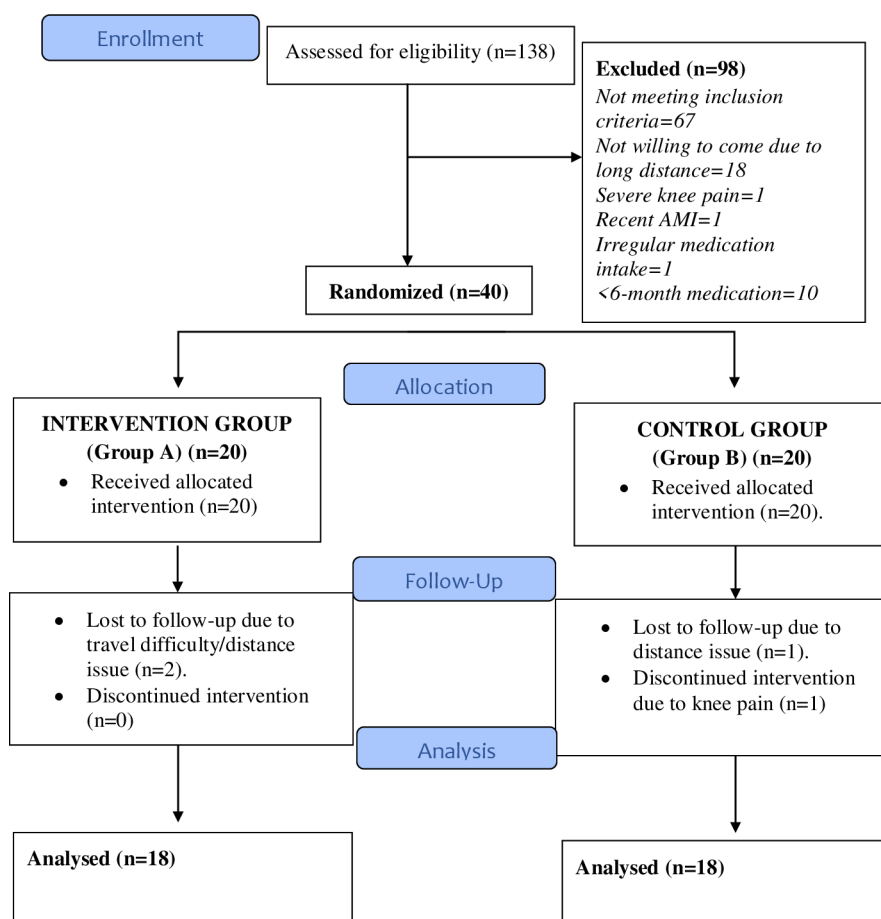


**Figure 1** CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials; AMI, Acute Myocardial Infarction.

**Table 1** Structured exercise prescription for early-stage Parkinson's disease for intervention group

| (A) Exercise prescription | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Each exercise session (40 min)** | **Each week** | | | | | | |
| | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** |
| Warm-up (5 min) | Trunk mobility exercise | Trunk mobility exercise | Trunk mobility exercise | Trunk mobility exercise | Trunk mobility exercise | Trunk mobility exercise | Trunk mobility exercise |
| Conditioning (30 min) | Strengthening exercise | Aerobic exercise | Agility exercise | Strengthening exercise | Aerobic exercise | Agility exercise | Aerobic exercise |
| Cool-down (5 min) | Active stretching exercises | Active stretching exercises | Active stretching exercises | Active stretching exercises | Active stretching exercises | Active stretching exercises | Active stretching exercises |

| (B) Strengthening exercises | | |
|---|---|---|
| On standing | Wall slides | Stand with feet 6–8 inches from the wall. |
| | | Rest your back and hands on the wall. |
| | | Slowly bend your knees and slide down the wall. |
| | | Do not let your knees move past your feet. |
| | | Hold this pose for a count of 5. |
| | Quad strengthening | Sit tall on the edge of a chair with your arms crossed on your chest. |
| | | Slowly lean forward and use your legs to push up to stand. |
| | | Stand for a moment. |
| | | Slowly lean forward again and lower yourself to sit. |
| Sitting | Shoulder blade squeeze | Sit tall on edge of chair. |
| | | Open arms out to the sides, fingers spread. |
| | | Pull arms back and squeeze shoulder blades together. |
| On-the-ground/supine | Bridge | Lie on back with knees bent and feet flat. |
| | | Raise hips and squeeze buttocks. |
| | | Hold this pose for a count of 5. |
| | Quadruped | Begin on hands and knees. Keep back level. |
| | | Reach one arm straight forward. |
| | | Extend opposite leg straight back. |
| | | Hold for a count of 3–5. |
| | | Repeat on other side. |
| | Back extension | Lie on stomach. |
| | | Lift upper body off surface, supporting body weight on forearms. |
| | | Hold position for 5–10 counts. |
| | | NOTE: this is not a push-up. Your back muscles should be doing the work, not your arms. |

| (C) Trunk exercises | | |
|---|---|---|
| **Task** | **Movements** | **Repetitions/progression** |
| Trunk mobility exercises for warm up | Lateral bends | 10 to the left 10 to the right |
| | Torso rotations | 10 to the left 10 to the right |
| | Small arm circles | 10 forwards 10 backward |
| | Large arm circles | 10 forwards 10 backward |
| | Torso rotations with high and low reaching | 10 reaching up to left, down to right |
| | | 10 reaching up to right, down to left |
| Exercises for active cool down | Hamstring stretches | Two sets of 20s holds |
| | Quadriceps stretch | Two sets of 20s holds |
| | Gastrocnemius/soleus stretch | Two sets of 20s holds |
| | Triceps stretch | Two sets of 20s holds |
| | Pectoral stretch | Two sets of 20s holds |

**Table 2** Stretching exercises for control group

| | Area of stretching | Steps | Dosing (total 30 min each day, 3 days/week) | Home advice |
|---|---|---|---|---|
| *On standing* | | | | |
| 1 | Chest stretch | 1. Stand facing a corner, placing forearms and hands on each wall. 2. Learn forward into the corner. 3. Keep head up and feet flat on the floor. | Hold stretches for 10–30 s. Perform 2–3 repetitions of each stretch. | 1. Your stretch should feel like a gentle pull. Do not stretch to the point of pain. 2. Remain motionless while holding your stretch. Do not bounce while stretching. 3. Breathe evenly in and out during each stretch. Do not hold your breath. |
| 2 | Back stretch | 1. Stand with feet hip-width apart. 2. Place palms on low back. 3. Gently lean trunk and neck back. | Same | Same |
| 3 | Shoulder stretch | 1. Stand tall with feet hip width apart. 2. Clasp hands behind back. 3. Gently lift arms up and away from the back, keeping head up. | Same | Same |
| *Sitting* | | | | |
| 1 | Neck and chest stretch | 1. Sit tall in a chair with hands clasped behind back of chair. 2. Allow neck to gently fall back. | Same | Same |
| 2 | Hamstring stretch | 1. Sit tall in chair and place one leg straight out on another chair. 2. Keep toes pointed up, knees flat and back straight. 3. Gently reach for toes. 4. Only reach as far forward as you can without your knee bending. | Same | Same |
| 3 | Rotation stretch | 1. Sit tall in a chair with one arm behind the chair. 2. Reach around in front of you with other arm to grab the back of chair or the arm rest. 3. Turn your neck and look over your shoulder. | Same | Same |
| 4. | Overhead stretch | 1. Sit tall in a chair and interlock fingers together. 2. Turn palms facing out and slowly lift arms overhead. 3. Gently allow neck to fall back. 4. Look up at hands. | Same | Same |
| 6 | Seated side stretch | 1. Sit to one side of a chair with arm rests. 2. Reach one arm down toward floor. 3. Reach other arm up and over to side. 4. Keep feet flat on floor. | Same | Same |
| *Supine* | | | | |
| 1 | Shoulder stretch | 1. Lie flat on your back. 2. If you are using a pillow, do not place it under your shoulders. 3. Slowly lift arms straight up and allow them to fall back overhead. | Same | Same |
| 2. | Rotation stretch | 1. Lie on your back with knees bent and feet flat. Arms should be outstretched at your side. 2. Rotate both knees to one side, keeping arms and upper torso flat. Turn head in opposite direction. 3. Repeat, rotating knees in the opposite direction. | Same | Same |

**Table 3** Demographic and baseline clinical characteristics

| Characteristics | Group A (n=20) | Group B (n=20) | P value |
|---|---|---|---|
| Age (year) | 57.5±12.1 | 52.3±12.5 | 0.19 |
| Sex (%) | Male: 12 (60%) | Male: 17 (85%) | 0.15 |
| | Female: 8 (40%) | Female: 3 (15%) | |
| PD diagnosis duration (month) | 19.1±9.9 | 17.7±9.8 | 0.78 |
| Duration of symptoms (month) | 32.9±16.6 | 27.8±12.6 | 0.46 |
| First symptom (%) | | | 0.10 |
| Tremor | 15 (75%) | 17 (85%) | |
| Bradykinesia | 5 (25%) | 1 (5%) | |
| Rigidity | 0 (0%) | 2 (10%) | |
| H&Y stage | | | 0.47 |
| Stage 1 | 1 (5%) | 2 (10%) | |
| Stage 1.5 | 9 (45%) | 5 (25%) | |
| Stage 2 | 10 (50%) | 13 (65%) | |
| Levodopa-carbidopa dosage amount/day (mg) | 434.3±191.5 | 411.2±176.7 | 0.69 |
| UPDRS | | | |
| UPDRS I | 3.6±1.8 | 3.5±2.2 | 0.77 |
| UPDRS II | 10.2±4.9 | 8.5±2.5 | 0.16 |
| UPDRS III | 21.8±7.1 | 19.5±5.3 | 0.20 |
| UPDRS VI | 0.68±0.1 | 0.67±0.1 | 0.80 |
| PDQL | 122.1±13.4 | 126.2±11.4 | 0.29 |

H&Y stage, Hoehn and Yahr stage; PD, Parkinson's disease; PDQL, Parkinson's disease quality of life; UPDRS, Unified Parkinson Disease's Rating Scale.

are on stable pharmacological regimens during the study period and for 6 months before entry into the study and are able to ambulate and function independently. Exclusion criteria were: patients having neurosurgical interventions, cognitive deterioration, psychiatric disturbances, neurological diseases other than PD, orthopaedic comorbidities that make exercises unsafe, any cardiac diseases contraindicating aerobic exercises and patients not willing to participate in the study.

Participants were randomised to both groups (1:1) via a remote computer-based randomisation system, which ensures concealment of the allocation sequence. Though blinding in non-pharmacological trials, especially exercise trials, is virtually impossible as interventions are obvious to those who receive them and sham procedures are not usually available, we tried a single-blind design. Randomisation is performed by a research assistant (statistician) who is not involved in the assessments or the data analysis. Group allocation was done by a separate doctor not involved in the assessment and intervention. The data analysis was done by a separate statistician. All the study personnel involved in the screening and assessments and the researcher who analysed the data were blinded to the allocation.

## Assessments
Basic demographic characteristics were collected at baseline. A thorough assessment was done to confirm the diagnosis by UKPD Society brain bank criteria, and H&Y staging was done. A detailed baseline evaluation was done by the UPDRS section III score (motor section) and also by UPDRS sections I, II, VI and PDQL.[13 14] Similar assessments of UPDRS were done at 4, 8 and 12 weeks, and assessments of PDQL were done at baseline and at 12 weeks. Assessment was done 1–2 hours following their scheduled dose of anti-parkinsonian medication (the 'on' medication state) to ensure a fair comparison with baseline assessments.

## UPDRS and PDQL
UPDRS is a validated rating instrument for PD with six segments. Reduction of scores indicates improvement. UPDRS total includes UPDRS I, II and III. Minimal clinically important difference (MCID) values are 2 for UPDRS activities of daily living (ADL), 5 for UPDRS III and 8 for UPDRS total. Motor scores show CIDs of 2.5 (minimal), 5.2 (moderate) and 10.8 (large). UPDRS total score estimates are 4.3 (minimal), 9.1 (moderate) and 17.1 (large) for CIDs. PDQL is a scale covering four PD domains (parkinsonian symptoms, systemic symptoms, social functioning and emotional functioning).

## Rationale for the CG[16 17]
There is compelling evidence of the benefits of exercise in PD, so a 'no exercise control group' may seem unethical. Hence, a CG where participants were doing only

**Table 4** Primary outcome measure (UPDRS III)

| UPDRS III* | Intervention group (IG) | Control group (CG) | Difference between mean scores (95% CI) | P value |
|---|---|---|---|---|
| Baseline | | | | |
| ITT | 21.85±7.08 | 19.3±5.26 | 2.55 (−1.44 to 6.54) | 0.20 |
| PP | 21.55±7.26 | 19.22±4.83 | 2.33 (−1.84 to 6.51) | 0.26 |
| Week 4 | | | | |
| ITT | 16.6±7.89† | 18.75±6.47 | −2.15 (−6.77 to 2.47) | 0.35 |
| PP | 16.38±8.31 | 17.55±5.61 | −1.17 (−5.97 to 3.64) | 0.62 |
| Week 8 | | | | |
| ITT | 15.8±7.73†‡ | 19.9±6.04 | −4.1 (−8.54 to 0.34) | 0.06 |
| PP | 15.5±8.11 | 18.83±5.33 | −3.33 (−7.98 to 1.32) | 0.15 |
| Week 12 | | | | |
| ITT | **15.35±7.27†‡§** | **20.4±6.23** | **−5.05 (−9.38 to −0.71)** | **0.02** |
| Reduction in UPDRS III from baseline (95% CI) | **6.5 (4.85 to 8.14)¶** | **−0.8 (−3.06 to 1.46)** | **7.3 (4.59 to 10.00)** | **<0.001** |
| PP | **15±7.60** | **19.38±5.68** | **−4.38 (−8.93 to 0.16)** | 0.058 |
| Reduction in UPDRS III from baseline (95% CI) | **6.55 (4.83 to 8.27)¶** | **−0.16 (−1.00 to 1.33)** | **6.38 (4.38 to 8.39)** | **<0.001** |

Details of repeated measure analysis are available in online supplemental table 1.
Bold values highlight the 12 weeks UPDRS is the primary outcome measure.
*UPDRS III: motor section of UPDRS.
†Repeated measure analysis between baseline and 4 weeks (statistically significant—intervention group: UPDRS I, II, III, Total), 8 weeks (statistically significant—intervention group: UPDRS I, II, III, Total) and 12 weeks (statistically significant—intervention group: UPDRS I, II, III, Total, VI).
‡Repeated measure analysis between 4 weeks and 8 weeks (statistically significant—UPDRS III in both groups; control group: UPDRS total), 12 weeks (statistically significant—intervention group: UPDRS Total, VI; control group: UPDRS I, III, Total).
§Repeated measure analysis between 8 weeks and 12 weeks (statistically significant: UPDRS III).
¶Minimal clinically important differences (MCID).
ITT, intention-to-treat; PP, per protocol; UPDRS, Unified Parkinson's Disease Rating Scale.

their regular daily activities and passive range of motion (stretching exercises) was planned. This group served as a CG (stretching exercise CG) with the IG.

## Intervention

All the interventions were selected in accordance with the ethical standards of the institutional committee. Exercises were demonstrated, practiced step by step and taught sufficiently so that participants could do them in their home environment. Exercises were supervised by a specialist doctor in Physical Medicine and Rehabilitation (PMR) and demonstrated by a senior physiotherapist. IG was allotted high-intensity exercises (aerobic, strengthening and agility exercises), and the other group served as the CG. Special emphasis was placed on health education to deal with motor problems in PD for both groups. Participants were demonstrated, taught exercises at the beginning of the rehabilitation setting and advised to follow those exercise prescriptions regularly at home as assigned to them. Participants were advised to keep an exercise diary regarding the exercises they did. At the end of 4 weeks, 8 weeks and lastly, 12 weeks, participants were reviewed and re-evaluated.

## Adherence and adverse events surveillance

Two PMR physicians (not involved in the assessment) supervised exercise adherence and monitored adverse events. Participants were instructed to maintain an exercise diary and report any adverse events to the respective PMR specialists. PMR physician contacted participants

daily to discuss the exercises performed that day to check adherence.

### Group-A (IG)

Exercises included strengthening, aerobic, agility and trunk exercises. In this group, participants were prescribed a weekly programme of structured exercises, in the format described in table 1A. Each day, each exercise session constituted of warm-up and cool-down (5 min each). The rest of the 30 min consisted of strengthening, aerobic and agility exercises (table 1A).

### Strengthening exercises

Dosing: one set of each exercise, 10 times, 2 days/week, 30 min/day.

Home advice: rest muscles before working them again; stop painful exercises; maintain good posture; avoid gripping weights tightly; breathe evenly during exercises; exhale during the hardest part, inhale during the easiest (table 1B).[18]

### Aerobic exercises

30 min/day walking for 3 days/week (intensity of walking according to patient's ability) with long steps, a normal base of support and arm swing.

### Agility exercise programme (clock lunges)[19]

Exercises: lunges with clock stepping.

Action (total 30 min, 2 days/week): Participants lean until their centre of mass is outside the base of support
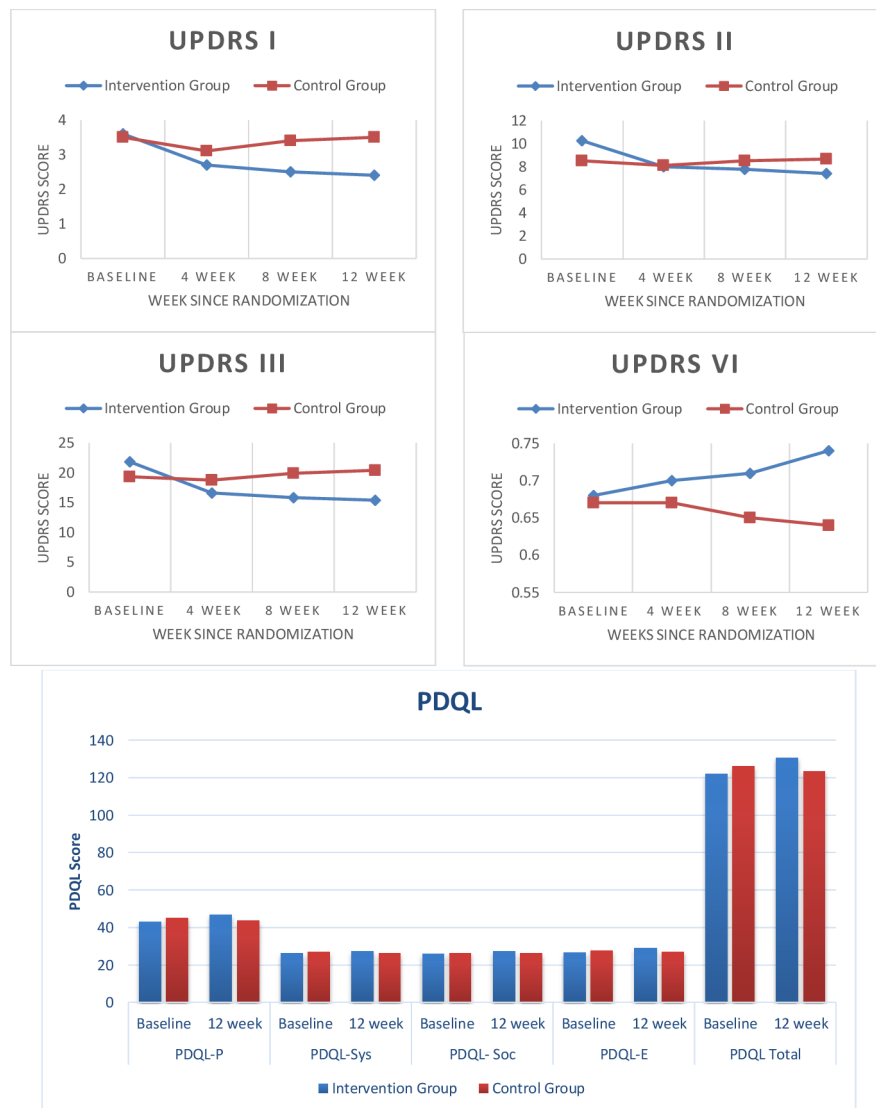
**Figure 2** Changes in UPDRS and PDQL in both groups. PDQL, Parkinson's Disease Quality of Life; UPDRS, Unified Parkinson's Disease Rating Scale.

and take a step. This is repeated in multiple directions (clock stepping).

### Trunk exercises
Trunk mobility exercises for warm-up and exercises for active cool-down are given in table 1C.[20 21]

### Group-B (CG)
Stretching exercises (passively done with the help of a case partner) are given in the table 2.[18]

### For both group A and group B: home advice for self-management
Self-managing health education regarding specific problems in PD was advised to be maintained at home by the participants in addition to all exercise.[18]

### Statistical analysis
There were no previous studies involving such structured exercises in early-stage PD. A study by Fisher *et al*[22] reported a reduction of 3 points (27.6±10.3 to 24.8±4.0)

in the UPDRS motor section in a high-intensity exercise intervention for 8 weeks among H&Y 1 or 2 stages of PD. As we proposed intervention for 12 weeks, we expected more improvements in the UPDRS motor section. Assuming the IG shows a reduction of 5 points, we calculated the sample size. Assuming an SD of 5, to detect this reduction in a two-sided t-test with 80% power and 5% α error, we required 16 patients per group. Considering the 25% drop-out rate, we randomised 40 participants to two groups.

Data were entered in a Microsoft Excel spreadsheet (Microsoft Corporation, New York, USA), and statistical analysis was done using Stata V.14 (StataCorp LLC, College Station, USA). Data were presented as mean±SD/median (range, min, max) and frequency percentage. Intention-to-treat (ITT) analysis was carried out by the last observation/value carried forward imputation method. For comparison, per protocol (PP) analysis was also carried out. Categorical variables were compared by $\chi^2$ or Fisher's exact test. Continuous variables were compared by

**Table 5** Secondary outcome measures (UPDRS I, II, VI and UPDRS Total)

| UPDRS | Intervention group (Group A) (ITT: n=20, PP: n=18) | Control group (Group B) (ITT: n=20, PP: n=18) | P value |
|---|---|---|---|
| *UPDRS I** | | | |
| Baseline | | | |
| ITT | 3.6±1.84 | 3.5±2.16 | 0.772 |
| PP | 3.3±1.81 | 3.2±2.07 | 0.721 |
| Week 4 | | | |
| ITT | 2.7±1.92† | 3.1±1.94 | 0.461 |
| PP | 2.5±1.97 | 2.7±1.73 | 0.490 |
| Week 8 | | | |
| ITT | 2.5±1.63†‡ | 3.4±1.78 | 0.084 |
| PP | 2.3±1.64 | 3.1±1.60 | 0.080 |
| Week 12 | | | |
| ITT | 2.4±1.46†‡§ | 3.5±1.73 | **0.035** |
| Reduction in UPDRS I from baseline (95% CI) | *1.15 (0.68 to 1.61)* | *0 (−0.54 to 0.54)* | **0.002** |
| PP | 2.2±1.43 | 3.2±1.55 | **0.031** |
| Reduction in UPDRS I from baseline (95% CI) | *1.11 (0.60 to 1.61)* | *0 (−0.61 to 0.61)* | **0.006** |

| | Intervention group | Control group | Difference between mean scores (95% CI) | P Value |
|---|---|---|---|---|
| *UPDRS II* | | | | |
| Baseline | | | | |
| ITT | 10.25±4.90 | 8.5±2.48 | 1.75 (−0.73 to 4.23) | 0.162 |
| PP | 10.05±4.72 | 8.11±2.29 | 1.94 (−0.57 to 4.45) | 0.125 |
| Week 4 | | | | |
| ITT | 8±3.86† | 8.1±2.48 | −0.1 (−2.18 to 1.98) | 0.923 |
| PP | 7.94±3.99 | 7.66±2.22 | 0.27 (−1.91 to 2.46) | 0.798 |
| Week 8 | | | | |
| ITT | 7.75±3.65†‡ | 8.5±2.6 | −0.75 (−2.80 to 1.30) | 0.464 |
| PP | 7.66±3.75 | 8.11±2.54 | −0.44 (−2.61 to 1.72) | 0.680 |
| Week 12 | | | | |
| ITT | 7.4±3.42†‡§ | 8.65±2.79 | −1.25 (−3.25 to 0.75) | 0.213 |
| Reduction in UPDRS II from baseline (95% CI) | **2.85 (1.74 to 3.95)¶** | **−0.15 (−0.81 to 0.51)** | **3 (1.74 to 4.25)** | **<0.001** |
| PP | 7.27±3.49 | 8.27±2.69 | −1 (−3.11 to 1.11) | 0.343 |
| Reduction in UPDRS II from baseline (95% CI) | **2.77 (1.69 to 3.86)¶** | **−0.16 (−0.91 to 0.58)** | **2.94 (1.67 to 4.21)** | **<0.001** |
| *UPDRS VI* | | | | |
| Baseline | | | | |
| ITT | 0.68±0.06 | 0.67±0.05 | 0.005 (−0.03 to 0.04) | 0.802 |
| PP | 0.68±0.07 | 0.67±0.05 | 0.005 (−0.03 to 0.04) | 0.793 |
| Week 4 | | | | |
| ITT | 0.70±0.07† | 0.67±0.05 | 0.03 (−0.01 to 0.07) | 0.178 |
| PP | 0.7±0.07 | 0.67±0.05 | 0.02 (−0.01 to 0.07) | 0.227 |
| Week 8 | | | | |
| ITT | 0.71±0.07†‡ | 0.65±0.05 | 0.06 (0.02 to 0.09) | **0.004** |
| PP | 0.71±0.06 | 0.65±0.05 | 0.06 (0.02 to 0.10) | **0.004** |
| Week 12 | | | | |
| ITT | 0.74±0.05†‡§ | 0.64±0.05 | 0.09 (0.05 to 0.13) | **0.000** |
| Reduction in UPDRS VI from baseline (95% CI) | *−0.06 (−0.08 to −0.03)* | *0.03 (0.00 to 0.05)* | *−0.09 (−0.13 to −0.05)* | **0.000** |
| PP | 0.74±0.05 | 0.64±0.05 | 0.1 (0.06 to 0.13) | **0.000** |

Continued

**Table 5**  Continued

| | Intervention group | Control group | Difference between mean scores (95% CI) | P Value |
|---|---|---|---|---|
| Reduction in UPDRS VI from baseline (95% CI) | *−0.06 (−0.09 to −0.03)* | *0.03 (0.003 to 0.06)* | *−0.09 (−0.13 to −0.05)* | **0.000** |
| | **Intervention group** | **Control group** | | **P value** |
| *UPDRS Total (I, II, III)* | | | | |
| Baseline | | | | |
| ITT | 35.7±12.98 | 31.3±7.54 | | 0.197 |
| PP | 35±12.99 | 30.5±7.20 | | 0.213 |
| Week 4 | | | | |
| ITT | 27.3±12.66† | 29.95±9.87 | | 0.465 |
| PP | 26.9±13.28 | 28±8.24 | | 0.765 |
| Week 8 | | | | |
| ITT | 26.0±12.03†‡ | 31.8±9.33 | | 0.099 |
| PP | 25.5±12.56 | 30.05±8.02 | | 0.203 |
| Week 12 | | | | |
| ITT | 25.2±11.16†‡§ | 32.6±9.16 | | **0.030** |
| Reduction in UPDRS Total from baseline (95% CI) | *10.55 (7.66 to 13.44)¶* | *−1.25 (−4.04 to 1.54)* | | 0.068 |
| PP | 24.5±11.56 | 30.9±8.57 | | |
| Reduction in UPDRS Total from baseline (95% CI) | *10.5 (7.55 to 13.44)¶* | *−0.33 (−2.56 to 1.89)* | | |

Details of repeated measure analysis are available in online supplemental table 1.
*For values not normally distributed, only mean±SD are shown.
†Repeated measure analysis between baseline and 4 weeks (statistically significant—intervention group: UPDRS I, II, III, Total), 8 weeks (statistically significant—intervention group: UPDRS I, II, III Total) and 12 weeks (statistically significant- Intervention group: UPDRS I, II, III, Total, VI).
‡Repeated measure analysis between 4 weeks and 8 weeks (statistically significant- UPDRS III in both groups; Control group: UPDRS Total), 12 weeks (statistically significant-Intervention group: UPDRS Total, VI; Control group: UPDRS I, III, Total).
§Repeated measure analysis between 8 weeks and 12 weeks (statistically significant: UPDRS III).
¶Minimal clinically important differences (MCID).
ITT, intention-to-treat; PP, per protocol; UPDRS, Unified Parkinson's Disease Rating Scale.

independent t-test, and the difference between the two groups was reported with a 95% CI. On the other hand, the continuous variables not following the normal distribution were compared by the Wilcoxon rank-sum test. P value <0.05 was considered statistically significant.

## RESULTS

A total of 40 patients were randomised into groups A (IG) and B (CG). Four patients were lost to follow-up (one after 4 weeks and one after 8 weeks in each group). Thirty-six patients completed 12-week follow-up, 18 in each group. No significant differences were identified at baseline with respect to age, sex, H&Y stage, UPDRS sections or PDQL between the two groups.

## Participants characteristics

The majority (72.5%) of patients belonged to the 40–65 year-old age group. 12.5% of patients among the 40 were diagnosed with young-onset PD. At the beginning of the study, there were 23 patients (57.5%) in H&Y stage 2 and 14 patients (35%) in H&Y stage 1.5 and 3 patients (7.5%) were in H&Y stage 1. Baseline demographic characteristics are shown in table 3.

## Primary outcome measure
### UPDRS III

At baseline, there was no significant between-group difference (mean difference: 2.55 points, 95% CI (−1.44 to 6.54)]. At 4 weeks and 8 weeks, there were no significant differences (mean difference: −2.15 points (95% CI: −6.77 to 2.47) and −4.1 points (95% CI: −8.54 to 0.34), respectively). But at 12 weeks, a significant difference was found (mean difference: −5.05 points (95% CI: −9.38 to −0.71), p=0.02) (table 4; figure 2). A gradual decline in the mean score was seen in the CG (group B). Furthermore, within-group analysis was done. In the IG, there was a 6.5 points reduction from baseline to 12 weeks (95% CI (4.85 to 8.14)); on the other hand, the CG showed an increase of 0.8 points (95% CI (−3.06 to 1.46)). The difference between the within-group changes was also significant (difference: 7.3 points; 95% CI (4.59 to 10.00); p 0.001). Repeated measure analysis showed statistically significant improvement in the IG from baseline to 4 weeks, from 4 to 8 weeks and from 8 weeks to 12 weeks. In CG, statistically significant decline from 4 weeks to 8 and 12 weeks was observed but from baseline to 12 weeks the decline was not statistically significant (table 4, online supplemental table 1).

**Table 6** Secondary outcome measure (PDQL)

| PDQL | Intervention group (IG) | Control group (CG) | Difference between mean scores (95% CI) | P value |
|---|---|---|---|---|
| *PDQL—Parkinsonian symptoms* | | | | |
| Baseline | | | | |
|   ITT | 43.15±6.18 | 45.2±5.67 | −2.05 (−5.84 to 1.74) | 0.281 |
|   PP | 43.11±6.14 | 45.88±5.55 | −2.77 (−6.74 to 1.18) | 0.163 |
| Week 12 | | | | |
|   ITT | 46.75±6.28 | 43.75±5.37 | 3 (−0.74 to 6.74) | 0.113 |
|   Reduction from baseline (95% CI) | *−3.6 (−5.46 to −1.73)* | *1.45 (−0.04 to 2.94)* | *−5.05 (−7.35 to −2.74)* | *<0.001* |
|   PP | 47.11±6.14 | 44.27±5.41 | 2.83 (−1.08 to 6.75) | 0.151 |
|   Reduction from baseline (95% CI) | −4 (−5.98 to −2.01) | 1.61 (−0.04 to 3.26) | −5.61 (−8.10 to −3.11) | 0.000 |
| *PDQL—systemic symptoms* | | | | |
| Baseline | | | | |
|   ITT | 26.15±2.41 | 26.95±1.84 | −0.8 (−2.17 to 0.57) | 0.246 |
|   PP | 26.22±2.53 | 27.0±1.79 | −0.83 (−2.32 to 0.65) | 0.263 |
| Week 12 | | | | |
|   ITT | 27.45±2.3 | 26.45±1.98 | 1 (−0.40 to 2.40) | 0.156 |
|   Reduction from baseline (95% CI) | *−1.3 (−2.04 to −0.55)* | *0.3 (−0.01 to 0.60)* | *−1.6 (−2.37 to −0.82)* | *<0.001* |
|   PP | 27.66±2.40 | 26.5±1.97 | 1.16 (−0.32 to 2.65) | 0.120 |
|   Reduction from baseline (95% CI) | −1.44 (−2.24 to −0.64) | 0.33 (−0.01 to 0.67) | −1.77 (−2.61 to −0.93) | 0.000 |
| *PDQL—social functioning* | | | | |
| Baseline | | | | |
|   ITT | 26.05±1.90 | 26.45±2.35 | −0.4 (−1.76 to 0.96) | 0.557 |
|   PP | 26.22±1.92 | 26.6±2.19 | −0.38 (−1.78 to 1.01) | 0.576 |
| Week 12 | | | | |
|   ITT | 27.4±2.3 | 26.15±2.60 | 1.25 (−0.32 to 2.82) | 0.117 |
|   Reduction from baseline (95% CI) | *−1.15 (−1.81 to −0.48)* | *0.3 (−0.24 to 0.84)* | *−1.45 (−2.28 to −0.61)* | *0.001* |
|   PP | 27.72±2.21 | 26.27±2.51 | 1.44 (−0.16 to 3.05) | 0.076 |
|   Reduction from baseline (95% CI) | −1.5 (−2.09 to −0.90) | 0.33 (−0.28 to 0.94) | −1.83 (−2.65 to −1.00) | 0.000 |
| *PDQL—emotional functioning* | | | | |
| Baseline | | | | |
|   ITT | 26.7±4.88 | 27.6±4.73 | −0.9 (−3.98 to 2.18) | 0.558 |
|   PP | 26.77±5.11 | 27.11±4.28 | −0.33 (−3.52 to 2.86) | 0.833 |
| Week 12 | | | | |
|   ITT | 28.9±4.68 | 27.1±4.99 | 1.8 (−1.30 to 4.90) | 0.247 |
|   Reduction from baseline (95% CI) | *−2.2 (−3.80 to −0.59)* | *0.5 (0.01 to 0.99)* | *−2.7 (−4.32 to −1.07)* | *0.000* |
|   PP | 29.22±4.79 | 26.55±4.52 | 2.66 (−0.49 to 5.82) | 0.095 |
|   Reduction from baseline (95% CI) | −2.44 (−4.20 to −0.68) | 0.55 (0.01 to 1.10) | −3 (−4.77 to −1.22) | 0.000 |
| *PDQL Total* | | | | |
| Baseline | | | | |
|   ITT | 122.05±13.41 | 126.2±11.39 | −4.15 (−12.11 to 3.81) | 0.298 |
|   PP | 122.33±13.76 | 126.66±11.44 | −4.33 (−12.90 to 4.24) | 0.311 |
| Week 12 | | | | |
|   ITT | 130.5±13.98 | 123.45±11.96 | 7.05 (−1.27 to 15.37) | 0.094 |
|   Reduction from baseline (95% CI) | *−8.45 (−12.78 to −4.11)* | *2.75 (0.16 to 5.33)* | *−11.2 (−16.08 to −6.31)* | *0.000* |

Continued

**Table 6** Continued

| PDQL | Intervention group (IG) | Control group (CG) | Difference between mean scores (95% CI) | P value |
|---|---|---|---|---|
| PP | 131.72±13.85 | 123.61±12.16 | 8.11 (−0.72 to 16.94) | 0.070 |
| Reduction from baseline (95% CI) | −9.38 (−14.01 to −4.76) | 3.05 (0.18 to 5.92) | −12.44 (−17.68 to −7.20) | 0.000 |

ITT, intention-to-treat; PDQL, Parkinson's Disease Quality of Life; PP, per protocol.

## Secondary outcome measures

### UPDRS I
The difference at 12 weeks was significant (p=0.03) (table 5, figure 2).

### UPDRS II
This section did not show any statistically significant between-group difference at 4 weeks (mean scores (95% CI), −0.1 (−2.18 to 1.98), p=0.92), 8 weeks (−0.75 (−2.80 to 1.30), p=0.46) or 12 weeks (−1.25 (−3.25 to 0.75), p=0.21) but the IG showed improvement in terms of a reduction in mean scores at the end of 12 weeks (MCID >2.5; 2.85 points (95% CI: 1.74 to 3.95)) (table 5, figure 2).

### UPDRS VI
It showed statistically significant between-group differences at 8 weeks (p=0.004) and 12 weeks (p=0.000). But at 4 weeks, improvement was not significant (p=0.178) (table 5, figure 2).

### UPDRS total
It includes UPDRS I, II and III. It showed a statistically significant between-groups difference at 12 weeks (p=0.03) (table 5).

### Parkinson's disease quality of life
At 12 weeks, the PDQL total did not show any statistically significant between-group difference (p=0.09) (table 6, figure 2). But within-group analysis showed 8.45 points increase from baseline to 12 weeks in the IG and 2.75 points reduction in the CG. The difference in within-group change was significant (p=0.00).

## Retention and adherence
Ninety per cent of individuals in the IG and CG (18 out of 20 participants) completed the trial. One hundred per cent of participants adhered to structured exercises in the IG, but two participants did not come for follow-up due to travel difficulties.

## Adverse events
There were no adverse events in either group.

## DISCUSSION
To the best of our knowledge, this is probably the first randomised controlled trial (RCT) to study the efficacy of structured exercises in early-stage PD.

Our study showed that there was statistically significant improvement in the motor section of the UPDRS score at 12 weeks but not at 4 weeks or 8 weeks in the IG. The MCID of UPDRS III is 5 points.[23] In our study, UPDRS III showed a −5.05-point mean difference at 12 weeks (95% CI: −9.38 to −0.71, p=0.02) and a 6.5-point reduction from baseline (from 21.85±7.08 to 15.35±7.27). Furthermore, repeated measure analysis showed significant improvement from baseline to 4, 8 and 12 weeks, as well as among all the time points for the primary objective of our study (UPDRS III) (online supplemental table 1). This implies that for significant motor improvement, exercises must be continued for at least 3 months. The CG showed a decline (from 19.3±5.26 to 20.4±6.23) in UPDRS III during follow-up which was statistically not significant. As, both groups were on stable pharmacological regimens, the result of our study implies that structured exercise has an effect on motor symptoms independent of levodopa. A recent delayed-start trial of levodopa in PD showed that levodopa has no disease-modifying effects,[24] further studies are needed to evaluate disease-modifying effects of structured exercises in early-stage PD. Recently, the Park-in-Shape trial also provided level 1 evidence that aerobic exercise can attenuate motor symptoms in PD.[16] Previous experimental studies on rodents also showed that exercise can alter the neurodegenerative process.[8] Though some previous studies showed significant improvement in UPDRS III after a training period of 6 months,[9] but our study showed improvement after 3 months of structured exercises. Probable reasons are, first, that our study population was early-stage PD, those who had no balance issues (H&Y stage 1 to 2), or dyskinesia. These participants may be more able to adhere to the exercise duration and intensity. Second, as levodopa has a dramatic effect on symptoms at the beginning, the effect of exercise may be similarly dramatic at the beginning.

The mentation, behaviour and mood sections of UPDRS (UPDRS I) also showed improvement in the IG after 3 months.

The ADL section of UPDRS (UPDRS II) in the IG did not show any significant improvement between groups, but the percentage ADL (UPDRS VI) showed significant improvement. This may be due to the percentage expression of ADL in UPDRS VI. Furthermore, the IG showed clinical improvement in terms of a reduction of mean scores (>2 points, MCID for UPDRS II: 2) in UPDRS II in every 4 weeks period; such improvement was not seen in

the CG. The UPDRS total also showed a 10.5-point reduction from baseline (MCID for the UPDRS total: 8).

The PDQL total in the IG did not show significant improvement between groups. Exercise intervention showed significant results in motor and ADL but not in the quality-of-life section; this may be due to the fact that the PDQL questionnaire is a patient-reported subjective scale whereas the UPDRS is an objective one. Many other factors in patients can have an impact on the alterations observed in PDQL.

A prospective 4-month follow-up study of structured exercises in moderately disabled PD showed improvement in UPDRS I, II, VI and PDQL total,[25] but our study of early-stage PD showed improvement in UPDRS I, III and VI only. It implies that the early institution of structured exercises can improve motor symptoms. In our study, although IG did not have improved PDQL scores than CG after 12 weeks, PDQL scores improved in the IG group but not the CG. Thus, a larger study may have greater power to detect a significant difference. Moreover, an 8-week study conducted among a similar population indicated the significance of dose-dependent advantages of exercise, especially high-intensity exercises, in fostering neuroplasticity.[22] Here, the researchers emphasised the necessity to identify fundamental 'exercise parameters' that facilitate motor enhancement. Within our 12-week study, we defined exercise parameters in detail including dosage, duration, timing and more, resulting in observable motor improvement.

Taking drop-outs into account, our PP analysis showed different results from ITT in UPDRS III only. PP analysis did not show a statistically significant result (p=0.058) in UPDRS III. PP analysis refers to the inclusion in the analysis of only those patients who strictly adhered to the protocol; it does not represent real-life situations. On the other hand, ITT closely represents clinical practice; hence, ITT is today considered a de facto standard for the analysis of clinical trials. It is often said that ITT represents the 'effectiveness' of interventions in RCTs, whereas PP represents the 'efficacy' of interventions in RCTs.[26] This finding is clinically important as UPDRS I and VI both showed significant results in both PP and ITT analysis, so it can be said that exercise is efficacious in improving those domains, whereas only ITT showed significant results in UPDRS III and not in PP analysis. It can be said that exercises showed 'effectiveness' in improving motor symptoms. Furthermore, PP analysis creates attrition bias, and efficacy trials depending only on PP analysis can give wrong information; hence, ITT analysis is also done in efficacy trials to give further information. In this perspective, both types of analysis gave insight into the actual efficacy of exercises in UPDRS III in clinical practice.

Exercise adherence and retention were good in our study. Retention was 90%, and one patient could not adhere to prescribed exercises due to knee pain (unrelated to exercise) in the CG and was lost follow-up for the same reason. No adverse events were reported related to exercise. Studies also showed similar adherence and retention in RCTs related to exercises in the PD population.[27] Our study had 10% dropouts whereas literature had 25%. The main reason for dropout was travel issues or distance like previous studies.[27]

Outcome measures that did not show between-group differences in our study were perhaps due to either good baseline values (creating possible ceiling effects) or small sample size. In our study, participants were taught exercises and advised to do them in their home environment. A recent study also showed that home-based exercises have a better impact.[28]

Our study has limitations that could be addressed in future research. First, we did not conduct a long-term follow-up beyond 12 weeks, which is necessary to understand the lasting effects of exercises on PD. Second, a larger sample size or more specific outcome measures would have been necessary to detect any differences in quality of life among individuals with PD. Third, we did not specifically focus on non-motor symptoms and their impact using other outcome measures. Lastly, although we implemented measures to minimise selection bias, conducting a single-centre study in a neurology clinic introduces the potential for selection bias.

We conclude that exercises are efficacious in improving mentation, ADL and motor symptoms in early-stage PD. Our results suggest that structured exercise has an impact on motor symptoms independent of levodopa. Furthermore, our findings imply that exercises in a structured format should be instituted as an early rehabilitation intervention in early-stage PD soon after the diagnosis. Exercises should be prescribed for a minimum of 12 weeks to have clinically significant effects. Future dose–response study of exercises with long-term effects and larger sample in early PD would be one of the research needs.

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**ORCID iD**
Raktim Swarnakar http://orcid.org/0000-0002-7221-2825

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